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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: COUSINS, Russell, Donovan [US/US]; 2053 Kings Row, Oxford, PA 19363 (US). ELLIOTT, John, Duncan [GB/US]; 723 Old Eagle School Road, Wayne, PA 19087 (US). LAGO, Maria, Amparo [ES/US]; 701 Pondview Drive, Audubon, PA 19403 (US). LEBER, Jack, Dale [US/US]; 403 Pine Run Road, Audubon, PA 19403 (US). PEISHOFF, Catherine, Elizabeth [US/US]; 1525 Richard Drive, West Chester, PA 19380 (US).

(74) Agents: HALL, Linda, E. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

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(54) Title: ENDOTHELIN RECEPTOR ANTAGONISTS

(57) Abstract

Novel indane and indene derivatives are described which are endothelin receptor antagonists.

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ENDOTHELIN RECEPTOR ANTAGONISTS

FIELD OF INVENTION

The present invention relates to novel indane and indene derivatives, pharmaceutical compositions containing these compounds and their use as endothelin receptor antagonists.

Endothelin (ET) is a highly potent vasoconstrictor peptide synthesized and released by the vascular endothelium. Endothelin exists as three isoforms, ET-1, ET-2 and ET-3. [Unless otherwise stated "endothelin" shall mean any or all of the isoforms of endothelin]. Endothelin has profound effects on the cardiovascular system, and in particular, the coronary, renal and cerebral circulation. Elevated or abnormal release of endothelin is associated with smooth muscle contraction which is involved in the pathogenesis of cardiovascular, cerebrovascular, respiratory and renal pathophysiology. Elevated levels of endothelin have been reported in plasma from patients with essential hypertension, acute myocardial infarction, subarachnoid hemorrhage, atherosclerosis, and patients with uraemia undergoing dialysis.

In vivo, endothelin has pronounced effects on blood pressure and cardiac output. An intravenous bolus injection of ET (0.1 to 3 nmol/kg) in rats causes a transient, dose-related depressor response (lasting 0.5 to 2 minutes) followed by a sustained, dose-dependent rise in arterial blood pressure which can remain elevated for 2 to 3 hours following dosing. Doses above 3 nmol/kg in a rat often prove fatal.

Endothelin appears to produce a preferential effect in the renal vascular bed. It produces a marked, long-lasting decrease in renal blood flow, accompanied by a significant decrease in GFR, urine volume, urinary sodium and potassium excretion. Endothelin produces a sustained antinatriuretic effect, despite significant elevations in atrial natriuretic peptide. Endothelin also stimulates plasma renin activity. These findings suggest that ET is involved in the regulation of renal function and is involved in a variety of renal disorders including acute renal failure, cyclosporine nephrotoxicity, radio contrast induced renal failure and chronic renal failure.

Studies have shown that in vivo, the cerebral vasculature is highly sensitive to both the vasodilator and vasoconstrictor effects of endothelin. Therefore, ET may be an important mediator of cerebral vasospasm, a frequent and often fatal consequence of subarachnoid hemorrhage.

ET also exhibits direct central nervous system effects such as severe apnea and ischemic lesions which suggests that ET may contribute to the development of cerebral infarcts and neuronal death.

ET has also been implicated in myocardial ischemia (Nichols et al. Br. J. Pharm. 99: 597-601, 1989 and Clozel and Clozel, Circ. Res., 65: 1193-1200, 1989) coronary vasospasm (Fukuda et al., Eur. J. Pharm. 165: 301-304, 1989 and Lüscher, Circ. 83: 701, 1991) heart failure, proliferation of vascular smooth muscle cells, (Takagi, Biochem & Biophys. Res. Commun.; 168: 537-543, 1990, Bobek et al., Am. J. Physiol. 258:408-C415, 1990) and atherosclerosis, (Nakaki et al., Biochem. & Biophys. Res. Commun. 158: 880-881, 1989, and Lerman et al., New Eng. J. of Med. 325: 997-1001, 1991). Increased levels of endothelin have been shown after coronary balloon angioplasty (Kadel et al., No. 2491 Circ. 82: 627, 1990).

Further, endothelin has been found to be a potent constrictor of isolated mammalian airway tissue including human bronchus (Uchida et al., Eur J. of Pharm. 154: 227-228 1988, LaGente, Clin. Exp. Allergy 20: 343-348, 1990; and Springall et al., Lancet, 337: 697-701, 1991). Endothelin may play a role in the pathogenesis of interstitial pulmonary fibrosis and associated pulmonary hypertension, Glard et al., Third International Conference on Endothelin, 1993, p. 34 and ARDS (Adult Respiratory Distress Syndrome), Sanai et al., Supra, p. 112.

Endothelin has been associated with the induction of hemorrhagic and necrotic damage in the gastric mucosa (Whittle et al., Br. J. Pharm. 95: 1011-1013, 1988); Raynaud's phenomenon, Cinniniello et al., Lancet 337: 114-115, 1991); Crohn's Disease and ulcerative colitis, Munch et al., Lancet, Vol. 339, p. 381; Migraine (Edmeads, Headache, Feb. 1991 p 127); Sepsis (Weitzberg et al., Circ. Shock 33: 222-227, 1991; Pittet et al., Ann. Surg. 213: 262-264, 1991), Cyclosporin-induced renal failure or hypertension (Eur. J. Pharmacol., 180: 191-192, 1990, Kidney Int, 37: 1487-1491, 1990) and endotoxin shock and other endotoxin induced diseases (Biochem. Biophys. Res. Commun., 161: 1220-1227, 1989, Acta Physiol. Scand. 137: 317-318, 1989) and inflammatory skin diseases. (Clin Res. 41:451 and 484, 1993).

Endothelin has also been implicated in preclampsia of pregnancy. Clark et al., Am. J. Obstet. Gynecol. March 1992, p. 962-968; Kamor et al., N. Eng. J. of Med., Nov 22, 1990, p. 1486-1487; Dekker et al., Eur J. Ob. and Gyn. and Rep. Bio. 40 (1991) 215-220; Schiff et al., Am. J. Ostet. Gynecol. Feb 1992, p. 624-628; diabetes mellitus, Takahashi et al., Diabetologia (1990) 33:306-310; and acute vascular rejection following kidney transplant, Watschinger et al., Transplantation Vol. 52, No. 4, pp. 743-746.

Endothelin stimulates both bone resorption and anabolism and may have a role in the coupling of bone remodeling. Tatrai et al. Endocrinology, Vol. 131, p. 603-607.

Endothelin has been reported to stimulate the transport of sperm in the uterine cavity, Casey et al., J. Clin. Endo and Metabolism, Vol. 74, No. 1, p. 223-225, therefore endothelin antagonists may be useful as male contraceptives. Endothelin modulates the ovarian/menstrual cycle, Kenegsberg, J. of Clin. Endo. and Met., Vol. 74, No. 1, p. 12, and may also play a role in the regulation of penile vascular tone in man, Lau et al., Asia Pacific J. of Pharm., 1991, 6:287-292 and Tejada et al., J. Amer. Physio. Soc. 1991, H1078-H1085. Endothelin also mediates a potent contraction of human prostatic smooth muscle, Langenstroer et al., J. Urology, Vol. 149, p. 495-499.

Thus, endothelin receptor antagonists would offer a unique approach toward the pharmacotherapy of hypertension, renal failure, ischemia induced renal failure, sepsis-endotoxin induced renal failure, prophylaxis and/or treatment of radio-contrast induced renal failure, acute and chronic cyclosporin induced renal failure, cerebrovascular disease, myocardial ischemia, angina, heart failure, asthma, atherosclerosis, Raynaud's phenomenon, ulcers, sepsis, migraine, glaucoma, endotoxin shock, endotoxin induced multiple organ failure or disseminated intravascular coagulation, cyclosporin-induced renal failure and as an adjunct in angioplasty for prevention of restenosis, diabetes, preclampsia of pregnancy, bone remodeling, kidney transplant, male contraceptives, infertility and priaprism and benign prostatic hypertrophy.

SUMMARY OF THE INVENTION

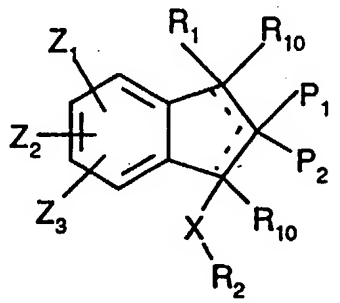
This invention comprises indane and indene derivatives represented by Formula (I) and pharmaceutical compositions containing these compounds, and their use as endothelin receptor antagonists which are useful in the treatment of a variety of cardiovascular and renal diseases including but not limited to:

hypertension, acute and chronic renal failure, cyclosporine induced nephrotoxicity, stroke, cerebrovascular vasospasm, myocardial ischemia, angina, heart failure, atherosclerosis, and as an adjunct in angioplasty for prevention of restenosis.

This invention further constitutes a method for antagonizing endothelin receptors in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of Formula (I).

DETAILED DESCRIPTION OF THE INVENTION

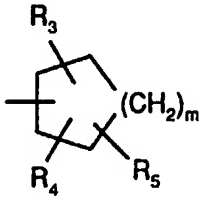
The compounds of this invention are represented by structural Formula (I):



(I)

wherein:

R_1 is $-X(CH_2)_nAr$ or $-X(CH_2)_nR_8$ or



(c);

R_2 is hydrogen, Ar, C_{1-4}alkyl, or (c);

P_1 is $-X(CH_2)_nR_8$;

P_2 is $-X(CH_2)_nR_8$, or -X-R_9-Y;

R_3 and R_5 are independently hydrogen, R_{11}, OH, C_{1-8}alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, Br, F, I, Cl, CF_3, $NHCOR_6$, $R_{11}CO_2R_7$, -X-R_9-Y, or $-X(CH_2)_nR_8$ wherein each methylene group within $-X(CH_2)_nR_8$ may be unsubstituted or substituted by one or two $-(CH_2)_nAr$ groups;

R_4 is hydrogen, R_{11}, OH, C_{1-5}alkoxy, $S(O)_qR_{11}$,$N(R_6)_2$, -$X(R_{11})$, Br, F, I, Cl or $NHCOR_6$ wherein the C_{1-5}alkoxy may be unsubstituted or substituted by OH, methoxy or halogen;

R_6 is independently hydrogen or C_{1-4}alkyl;

R_7 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-8}alkynyl all of which may be unsubstituted or substituted by one or more OH, $N(R_6)_2$, CO_2R_{12}, halogen or XC_{1-5}alkyl or R_7 is $(CH_2)_nAr$;

R_8 is hydrogen, R_{11}, CO_2R_7, $CO_2C(R_{11})_2$ $O(CO)XR_7$, $PO_3(R_7)_2$, $SO_2NR_7R_{11}$, $NR_7SO_2R_{11}$,$CONR_7SO_2R_{11}$, SO_3R_7, SO_2R_7, $P(O)(OR_7)R_7$, CN, $-CO_2(CH_2)_mC(O)N(R_6)_2$, $C(R_{11})_2N(R_7)_2$, $C(O)N(R_6)_2$, tetrazole or OR_6;

R_9 is $(CH_2)_n$, divalent C_{1-10}alkyl, divalent C_{2-10}alkenyl or phenyl, all of which may be unsubstituted or substituted by one or more OH, $N(R_6)_2$, COOH, halogen, or R_9 may be $\rangle C{=}O$ or XC_{1-5}alkyl;

R_{10} is R_3 or R_4;

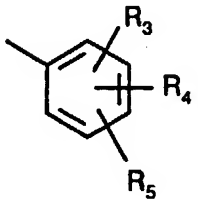
R_{11} is hydrogen, Ar, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, all of which may be unsubstituted or substituted by one or more OH, CH_2OH, $N(R_6)_2$ or halogen;

R_{12} is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-7}alkynyl;

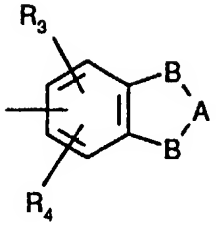
X is $(CH_2)_n$, O, NR_6 or $S(O)_q$;

Y is CH_3 or $X(CH_2)_nAr$;

Ar is:



(a)



(b)

naphthyl, indolyl, pyridyl, thienyl, oxazolidinyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl,

piperazinyl, pyrrolyl, or pyrimidyl; all of which may be unsubstituted or substituted by one or more R_3 or R_4 groups;

A is C=O, or $[C(R_6)2]_m$;

B is $-CH_2-$ or -O-;

Z_1 and Z_2 are independently hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, OH, C_{1-8}alkoxy, $S(O)qC_{1-8}$alkyl, $N(R_6)_2$, Br, F, I, Cl, $NHCOR_6$, $-X-R_9-Y$, $-X(CH_2)_nR_8$, phenyl, benzyl or C_{3-6}cycloalkyl wherein the C_{1-8}alkyl, C_{2-8}alkenyl or C_{2-8}alkynyl may be optionally substituted by COOH, OH, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R_6)_2$, or halogen; or Z_1 and Z_2 together may be -O-A-O- on contiguous carbons;

Z_3 is Z_1 or $-X-R_9-Y$;

q is zero, one or two;

n is an integer from 0 to six;

m is 1, 2 or 3;

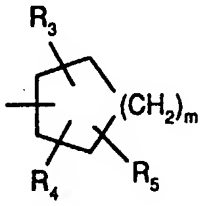
and the dotted line indicates the optional presence of a double bond; or a pharmaceutically acceptable salt thereof; provided that

- R_2 is not hydrogen when X is $S(O)_q$;
- when the optional double bond is present there is only one R_{10} and there is no P_1 and P_2 is not NR_6R_9Y;
- when the optional double bond is present and $X-R_2$ is attached to the double bond, X is not NR_6;
- when the optional double bond is present and R_1 is attached directly to the double bond, R_1 is not NR_6AR;
- when R_3, R_5, Z_1, Z_2, or Z_3 is $X(CH_2)_nR_8$ and n is not 0, X is oxygen or NR_6 when R_8 is OR_6 or CO_2H;
- when R_8 is $[CO(CR_{11})_2O(CO)XR_7]$ $CO_2C(R_{11})_2O(CO)XR_7$, X is not $S(O)_q$;
- the compound of Formula I is not (1RS)-1,3-diphenylindene-2-carboxylic acid; (cis,cis)-1,3-diphenylindane-2-carboxylic acid; (1RS)-3-[3-Methyl-1-phenyl-(1H)-ind-2-en-l-yl] propionic acid; or (1RS)-2[1,3-diphenyl-(1H)-ind-2-en-2-yl]ethanoic acid; 1,3-diphenyl-1-ethoxyindene-2-carboxylic acid; 1,2,3-triphenylindene; 1,3 diphenylindene; 1-(2,3-dimethyl-2-buten-yl)-1,3-diphenylindene; 1,3-diphenyl-2-methylindene; 1,3-diphenyl-2-methylindane; 1,3-diphenylindane; 5,6-dimethoxy-1,3-dimethoxyindene; 1,3-bis(4,5-dimethoxy-2-hydroxyphenyl)-5,6-dimethoxyindane; 1,3-bis(3,4-dimethoxyphenyl)-5,6-dimethoxyindane; 1,3-diphenyl-2-

methoxyidene, 1,3-diphenyl-2-ethoxyindene, 5-fluoro-2-methyl-indene-3-acetic acid;

and further provided that compounds wherein:

R_1 is $-X(CH_2)_nAr$ or $-X(CH_2)_nR_8$ or



(c);

R_2 is hydrogen, Ar or (c);

P_1 is $-X(CH_2)_nR_8$;

P_2 is $-X(CH_2)_nR_8$, or $-XR_9Y$;

R_3 and R_5 are independently hydrogen, R_{11}, OH, C_{1-8}alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, Br, F, I, Cl, CF_3, $NHCOR_6$, $-XR_9-Y$ or $-X(CH_2)_nR_8$ wherein the methylene groups of $-X(CH_2)_nR_8$ may be unsubstituted or substituted by one or more $-(CH_2)_nAr$ groups;

R_4 is hydrogen, R_{11}, OH, C_{1-5}alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, $-X(R_{11})$, Br, F, I, Cl or $NHCOR_6$ wherein the C_{1-5}alkoxy may be unsubstituted or substituted by OH, methoxy or halogen;

R_6 is independently hydrogen or C_{1-4}alkyl;

R_7 is independently hydrogen, C_{1-6}alkyl or $(CH_2)_nAr$;

R_8 is hydrogen, R_{11}, CO_2H, PO_3H_2, $P(O)(OH)R_7$ or tetrazole;

R_9 is C_{1-10}alkyl, C_{2-10}alkenyl or phenyl all of which may be unsubstituted or substituted by one or more OH, $N(R_6)_2$, COOH, halogen or XC_{1-5}alkyl;

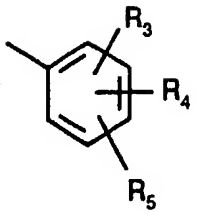
R_{10} is R_3 or R_4;

R_{11} is C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl all of which may be unsubstituted or substituted by one or more OH, CH_2OH, $N(R_6)_2$ or halogen;

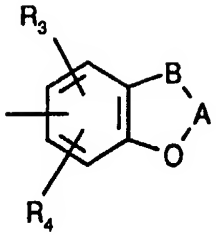
X is $(CH_2)_n$, O, NR_6 or $S(O)_q$;

Y is CH_3 or $-CH_2X(CH_2)_nAr$;

Ar is:



(a)



(b)

naphthyl, indolyl, pyridyl or thienyl, oxazolidinyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, or pyrimidyl; all of which may be unsubstituted or substituted by one or more R_3 or R_4 groups;

A is C=O, or $[C(R_6)_2]_m$;

B is $-CH_2-$ or -O-;

Z_1 and Z_2 are independently hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, OH, C_{1-8}alkoxy, $S(O)qC_{1-8}$alkyl, $N(R_6)_2$, Br, F, I, Cl, $NHCOR_6$, $-X(CH_2)_nR_8$, phenyl, benzyl or C_{3-6}cycloalkyl wherein the C_{1-8}alkyl, C_{2-8}alkenyl or C_{2-8}alkynyl may be optionally substituted by COOH, OH, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R_6)_2$, or halogen; or Z_1 and Z_2 together may be -O-A-O- on contiguous carbons;

Z_3 is Z_1 or XR_9Y;

q is zero, one or two;

n is an integer from 0 to six;

m is 1, 2 or 3; are excluded.

Also included in the invention are pharmaceutically acceptable salt complexes.

All alkyl, alkenyl, alkynyl and alkoxy groups may be straight or branched. The term "halogen" is used to mean iodo, fluoro, chloro or bromo. Alkyl groups may be substituted by one or more halogens up to perhalogenation.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and diastereoisomers are contemplated to be within the scope

of the present invention.

Preferred compounds are those wherein R_1 is $X(CH_2)_nAr$, (Ar is (a) or (b)), dihydrobenzofuranyl, benzodioxanyl, cyclohexyl, C_{1-4}alkyl; R_2 is (a), (b) C_{1-4}alkyl, indolyl or hydrogen; R_3 and R_5 are independently hydrogen, OH, C_{1-5}alkoxy, halogen, -OC_{1-4}alkyl phenyl, $R_{11}CO_2R_7$, C_{1-4}alkyl, $N(R_6)_2$, $NH(CO)CH_3$, -$X(CH_2)_nR_8$, -XR_9 pyridyl, phenyl or $S(O)_pC_{1-5}$alkyl; R_4 is hydrogen, OH, C_{1-5}alkoxy, halogen, C_{1-4}alkyl, $N(R_6)_2$, $NH(CO)CH_3$ or $S(O)_pC_{1-5}$alkyl; Z_1, Z_2 and Z_3 are independently XR_9Y, benzyl, hydrogen, OH, C_{1-5}alkoxy, -$N(R_6)_2$, $S(O)qC_{1-8}$alkyl, $NHCOR_6$, $X(CH_2)_nR_8$ or halogen, or Z_1 and Z_2 together may be -O-A-O on contiguous carbons; P_1 and P_2 are independently hydrogen, CO_2H or tetrazole; Ar is (a), (b), phenyl, or pyridyl; X is $(CH_2)_n$ or oxygen.

More preferred are compounds wherein R_3 is hydrogen or -$X(CH_2)_nR_8$, $R_{11}CO_2R_7$; R_4 and R_5 are independently hydrogen, OH, C_{1-5}alkoxy, SC_{1-5}alkyl, F, Br, C_{1-3}alkyl or NH_2; Z_1 and Z_3 are hydrogen and Z_2 is hydrogen, OH, C_{1-5}alkoxy, halogen, $X(CH_2)_nR_8$, NH_2, benzyl, $NH(CO)CH_3$, or Z_1 and Z_2 together may be O-A-O.

Most preferred are compounds wherein R_1 is (b) and R_2 is (a) or (b); A is CH_2, B is -O-; there is no optional double bond; R_1 and XR_2 are trans to P_1; Z_2 is OH, C_{1-5}alkoxy, -OCH_2CHCH_2 or hydrogen, Z_1 is hydrogen; R_3 is XAr, hydrogen, $X(CH_2)_qCOOH$, $X(CH_2)_qCONR_7SO_2R_{11}$ or $CH{=}CHCO_2H$, R_4 is hydrogen, substituted phenyl, or C_{1-2}alkoxy; and R_5, R_{10} and P_2 are hydrogen.

Also included are the following compounds:

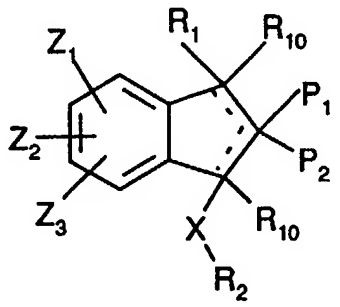
(+) (1S,2R,3S)-3-(2-Carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid;

(1RS, 2SR, 3RS)-3-[2-[(4-Carboxypyridin-3-yl)oxy]-4- methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid disodium salt;

(+) (1S, 2R, 3S)-3-[2-(2-Hydroxyeth-1-yloxy)-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid, dicyclohexylamine salt;

(1S, 2R, 3S)-3-[(2,2-dimethylpropanoyloxymethoxycarbonylmethoxy)-4-methoxy-phenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid sodium salt.

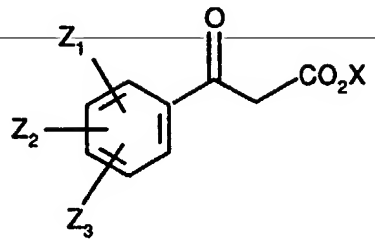
The present invention provides compounds of Formula (I) above



(I)

which can be prepared by a process which comprises:

a) reacting a compound of Formula (2) wherein X is C_{1-5}alkyl



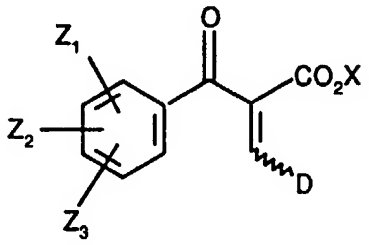
(2)

with a substituted benzaldehyde or aldehyde of Formula (3).

D-CHO

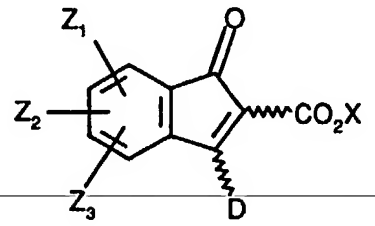
(3)

wherein D is Ar or (c) as defined in Formula I, in a suitable solvent such as benzene with a catalyst such as piperidinium acetate at reflux to provide a compound of Formula (4).



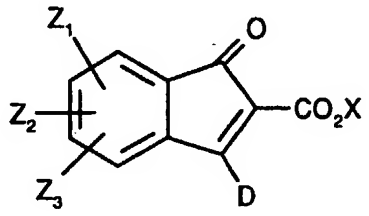
(4)

Cyclization of compound (4) in the presence of a suitable Lewis acid such as titanium tetracholoride or aluminum chloride or alternatively when Z_1 is 3-OR (meta)(where R is C_{1-5}alkyl, or benzyl), trifluoroacetic acid, provides an indanone of the Formula (5).



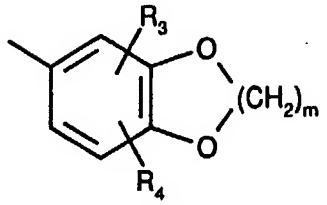
(5)

Dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in an appropriate solvent or alternatively bromination with pyridinium hydrobromide perbromide in dichloromethane followed by treatment with 1,5-diazabicyclo[4,3,0]non-5-ene provides indenones of Formula (6).

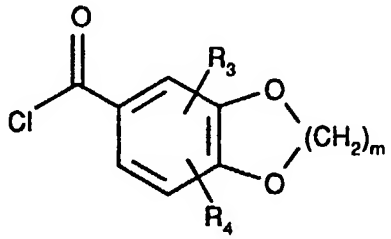


(6)

b) Alternatively, a compound of Formula 6 wherein Z_1, Z_2 and Z_3 are hydrogen and

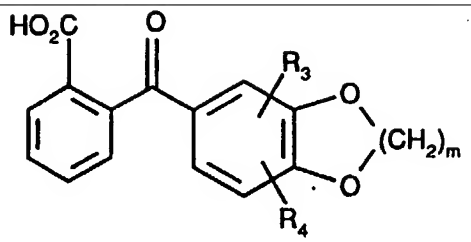
D= 

can be prepared by treatment of 2-bromobenzoic acid with two equivalents of n-butyllithium in a solvent such as tetrahydrofuran under argon at -78°C followed by the addition of an acid chloride of Formula (7):



(7)

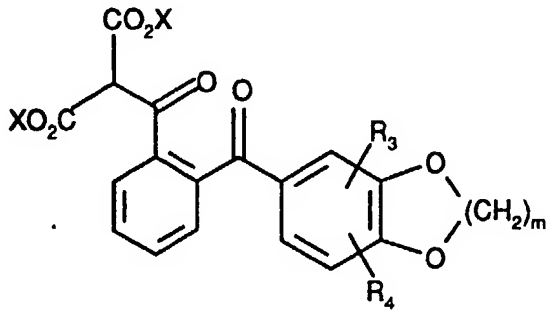
provides a compound of Formula (8):



(8)

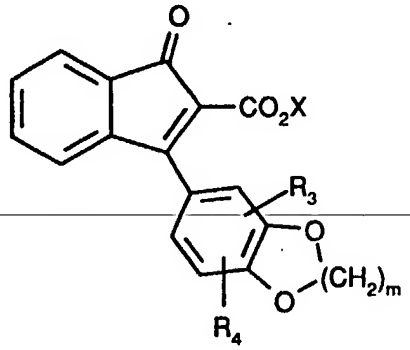
Treatment of compounds of type (8) with thionyl chloride at reflux gives an acid chloride which can be isolated by concentration under reduced

pressure. This acid chloride can then be treated with diethyl magnesium malonate in a solvent such as ether to give a compound of Formula (9):



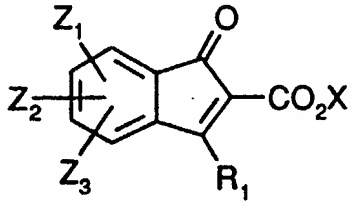
(9)

Reaction of a compound of type (9) at reflux with 5% aqueous sodium carbonate gives compounds of Formula (10):



(10)

c) Treatment of an indenone of Formula (11):

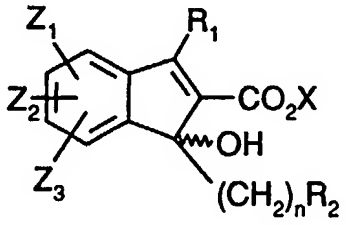


(11)

wherein Z_1, Z_2, Z_3 and R_1 are as defined for formula I or a group convertable to them, with an organomagnesium compound of Formula (12) wherein R_2 is defined for

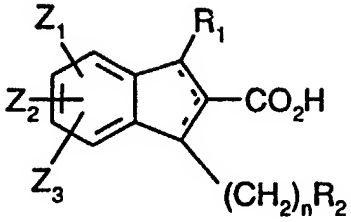
$$R_2(CH_2)_nMgBr \qquad (12)$$

Formula I or a group convertable to it, in a suitable solvent provides compounds of Formula (13):



(13)

Saponification of compounds of Formula (13) using sodium hydroxide in aqueous methanol followed by reduction with triethylsilane and boron trifluoride etherate in a suitable solvent such as dichloromethane at 0°C affords racemic compounds of Formula (14).

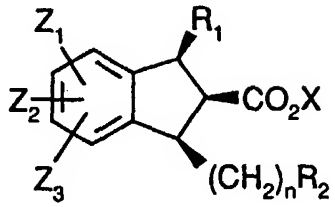


(14)

Conjugate addition of nucleophiles to an ester derived from Formula (14), followed by saponification affords compounds of Formula (I) having an R_{10} other than hydrogen. Re-introduction of a double bond into an ester derived from such acids followed by conjugate addition of another nucleophilic species and subsequent saponification affords compounds of Formula (1) in which neither R_{10} substituent is hydrogen.

Reduction of compounds of Formula (13) with triethylsilane and boron trifluoride etherate in a suitable solvent such as dichloromethane at 0°C followed by hydrogenation with hydrogen gas under pressure at approximately 60

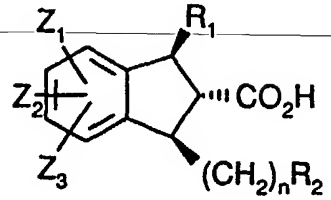
psi in the presence of a suitable catalyst such as 10% palladium on charcoal affords compounds of Formula (15):



(15)

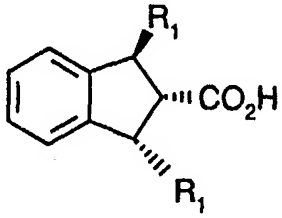
Alkylation or acylation of the ester enolate derived from Formula (15) affords compounds wherein P_1 and P_2 are as defined in Formula (1).

Alternatively, hydrogenation of compounds of Formula (13) with hydrogen gas under pressure at approximately 60 psi in the presence of a suitable catalyst such as 10% palladium on charcoal in a suitable solvent such as ethyl acetate or methanol containing 1-5% acetic acid affords compounds of Formula (15). Treatment of these compounds with a base such as sodium hydroxide in a suitable solvent such as aqueous ethanol provides racemic compounds of Formula (16):



(16)

wherein Z_1, Z_2 and Z_3 are hydrogen; $R_1 = R_2$; and n is 0.
Treatment of compounds of Formula (13) with triethylsilane and boron trifluoride etherate in a suitable solvent such as dichloromethane at 0°C followed by reaction with samarium II iodide in a suitable solvent such as tetrahydrofuran and then saponification, provides compounds of Formula (17)



(17)

With appropriate manipulation and protection of any chemical functionalities, synthesis of the remaining compounds of the Formula (I) is accomplished by methods analogous to those above and to those described in the Experimental section.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, transdermally, rectally, via inhalation or via buccal administration.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to themselves a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

I. Binding Assay

A) Membrane Preparation

Rat cerebellum or kidney cortex were rapidly dissected and frozen immediately in liquid nitrogen or used fresh. The tissues, 1-2 g for cerebellum or 3-5 g for kidney cortex, were homogenized in 15 mls of buffer containing 20mM

Tris HCl and 5mM EDTA, pH 7.5 at 4°C using a motor-driven homogenizer. The homogenates were filtered through cheesecloth and centrifuged at 20,000 x g for 10 minutes at 4°C. The supernatant was removed and centrifuged at 40,000 xg for 30 minutes at 4°C. The resulting pellet was resuspended in a small volume of buffer containing 50 mM Tris, 10 mM $MgCl_2$, pH 7.5; aliquotted with small vials and frozen in liquid nitrogen. The membranes were diluted to give 1 and 5 mg of protein for each tube for cerebellum and kidney cortex in the binding assay.

Freshly isolated rat mesenteric artery and collateral vascular bed were washed in ice cold saline (on ice) and lymph nodes were removed from along the major vessel. Then, the tissue was homogenized using a polytron in buffer containing 20 mM Tris and 5mM EDTA, pH 7.5 at 4°C in 15 ml volume for ~6 gm of mesenteric artery bed. The homogenate was strained through cheesecloth and centrifuged at 2,000 xg for 10 min. at 4°C. The supernatant was removed and centrifuged at 40,000 xg for 30 min. at 4°C. The resulting pellet was resuspended as explained above for cerebellum and kidney cortex. Approximately 10 mg of membrane protein was used for each tube in binding experiments.

B) [^{125}I]ET-1 Binding Protocol

[^{125}I]ET-1 binding to membranes from rat cerebellum (2-5 mg protein/assay tube) or kidney cortex (3-8 mg protein/assay tube) were measured after 60 minutes incubation at 30°C in 50 mM Tris HC1, 10 mM $MgCl_2$, 0.05% BSA, pH 7.5 buffer in a total volume of 100 ml. Membrane protein was added to tubes containing either buffer or indicated concentration of compounds. [^{125}I]ET-1 (2200 Ci/mmol) was diluted in the same buffer containing BSA to give a final concentration of 0.2-0.5 nM ET-1. Total and nonspecific binding were measured in the absence and presence of 100 nM unlabelled ET-1. After the incubation, the reactions were stopped with 3.0 ml cold buffer containing 50 mM Tris and 10 mM $MgCl_2$, pH 7.5. Membrane bound radioactivity was separated from free ligand by filtering through Whatman GF/C filter paper and washing the filters 5 times with 3 ml of cold buffer using a Brandel cell harvester. Filter papers were counted in a gamma counter with an efficiency of 75%. IC_{50}'s for the compounds of this invention range from 0.1 nm to 50 mm.

II. In Vitro Vascular Smooth Muscle Activity

Rat aorta are cleaned of connective tissue and adherent fat, and cut into ring segments approximately 3 to 4 mm in length. Vascular rings are suspended in organ bath chambers (10 ml) containing Krebs-bicarbonate solution of the following composition (millimolar): NaCl, 112.0; KC1, 4.7; KH_2PO_4, 1.2;

$MgSO_4$, 1.2; $CaCl_2$, 2.5; $NaHCO_3$, 25.0; and dextrose, 11.0. Tissue bath solutions are maintained at 37°C and aerated continuously with 95% 0_2/ 5% CO_2. Resting tensions of aorta are maintained at 1 g and allowed to equilibrate for 2 hrs., during which time the bathing solution is changed every 15 to 20 min. Isometric tensions are recorded on Beckman R-611 dynographs with Grass FT03 force-displacement transducer. Cumulative concentration-response curves to ET-1 or other contractile agonists are constructed by the method of step-wise addition of the agonist. ET-1 concentrations are increased only after the previous concentration produces a steady-state contractile response. Only one concentration-response curve to ET-1 is generated in each tissue. ET receptor antagonists are added to paired tissues 30 min prior to the initiation of the concentration-response to contractile agonists.

ET-1 induced vascular contractions are expressed as a percentage of the response elicited by 60 mM KCl for each individual tissue which is determined at the beginning of each experiment. Data are expressed as the mean ± S.E.M. Dissociation constants (K_b) of competitive antagonists were determined by the standard method of Arunlakshana and Schild. The potency range for compounds of this invention range from 0.1 nM to 50 mm.

The following examples are illustrative and are not limiting of the compounds of this invention.

EXAMPLE 1

(+) (1S,2R,3S)-3-(2-Carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid

a) 3-(Prop-1-yloxy)acetophenone. To a slurry of NaH (13.84 g, 0.58 mol) in dry DMF (50 mL) at 0°C, was added a solution of 3-hydroxyacetophenone (50 g, 0.37 mol). After stirring for 30 min. 1-iodopropane (70 mL, 0.72 mol) was added and the mixture stirred overnight at room temperature. The mixture was diluted with dry DMF (50 mL) and further NaH (2.77 g, 0.12 mol) added followed by 1-iodopropane (23 mL, 0.24 mol). After 1 h. TLC indicated that the reaction was complete and the product was cautiously quenched with 6M HCl and extracted with EtOAc. The EtOAc extract was washed successively with H_2O, 10% aqueous NaOH and then brine. After drying ($MgSO_4$), filtration and evaporation gave the title compound (65 g, 98%) as a light yellow oil which was used without further purification. Anal. Calc. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.89. Found: C, 73.85; H, 7.86.

b) Methyl 3-(Prop-1-yloxy)benzoylacetate. To a suspension of NaH (12 g, 0.5 mol) in dry dimethyl carbonate (50 mL) was added slowly a solution of 3-(Prop-1-yloxy)acetophenone (65 g, 0.37 mol) in dry dimethyl carbonate (100 mL). During the addition the exothermicity of the reaction caused refluxing. Following the addition the mixture was stirred mechanically overnight and was then quenched cautiously with 3M HCl and extracted with EtOAc. The EtOAc extract was washed successively with H_2O, 5% aqueous $NaHCO_3$, H_2O and brine. After drying ($MgSO_4$), filtration and evaporation gave a yellow oil (82 g, quantitative) which was used without further purification.

c) Methyl 3-(3,4-methylenedioxyphenyl)-2-[3-(prop-1-yloxy)-benzoyl]propenoate.To a solution of methyl 3-(prop-1-yloxy)benzoylacetate (10 g, 4.2 mmol) in benzene (50 mL) was added 3,4-methylenedioxybenzaldehyde (6.36 g, 4.2 mmol) followed by piperidine (0.42 mL, 0.42 mmol) and glacial acetic acid (8 drops approx.). The mixture was refluxed for 2 h. and the volatiles removed *in vacuo* to give methyl 3-(3,4-methylenedioxyphenyl)-2-[3-(prop-1-yloxy)-benzoyl]propenoate (7.4 g, 48%) as an off white solid after trituration with methanol (m. p. 122-123°C). Anal. Calc. for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.81; H, 5.49.

d) Methyl (1RS,2SR)-1-(3,4-Methylenedioxyphenyl)-5-(prop-1-yloxy)-3-oxo-indane-2-carboxylate. Methyl 3-(3,4-methylenedioxyphenyl)-2-[3-(prop-1-yloxy)-benzoyl]propenoate (7.4 g, 2.0 mmol) was dissolved in trifluoroacetic acid (50 mL) at 0°C and the mixture stirred at room temperature for 20 min. The trifluoroacetic acid was removed *in vacuo* to give the title compound (6.4 g, 87 %) as a white solid after trituration with warm isopropanol m. p. 106-108°C. Anal. Calc. for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.12; H, 5.41.

e) Methyl 3-(3,4-Methylenedioxyphenyl)-6-(prop-1-yloxy)-1-oxo-indene-2-carboxylate. Methyl (1RS, 2SR)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)-3-oxo-indane-2-carboxylate (26.2 g, 71 mmol) was dissolved in toluene (250 mL) and DDQ (dichlorodicyano-quinone) (16.5 g, 71 mmol) was added. The mixture was heated at 80°C for 2 h. then cooled, filtered and the solvent removed *in vacuo*. The product was purified by flash column chromatography on silica gel (eluant: EtOAc/hexane, 20:80) to give the title compound as an orange solid (11.3 g, 44 %); m.p. 125-126°C. Anal. Calc. for $C_{21}H_{18}O_6$: C, 68.85; H, 4.95. Found: C, 68.45; H, 4.97.

f) Methyl (1RS)-1-Hydroxy-1-(4-methoxy-2-methoxymethoxyphenyl)-3-(3,4-methylenedioxyphenyl)-6-(prop-1-yloxy)indene-2-carboxylate. To dry magnesium turnings (1.7 g, 69 mmol) under an argon atmosphere was added portionwise, a solution of 1-bromo-4-methoxy-2-methoxymethoxybenzene (16.8 g, 68 mmol) in 5% THF/ether (120 mL). The resulting 4-methoxy-2-methoxymethoxyphenyl magnesium bromide was added to a solution of methyl 3-(3,4-methylenedioxyphenyl)-6-(prop-1-yloxy)-1-oxo-indene-2-carboxylate (18.5 g, 51 mmol) in THF (400 mL) under an argon atmosphere at O°C. The resulting mixture was allowed to warm to room temperature and was stirred for 10 min. The mixture was partitioned between 3M HCl and EtOAc . The organic extract was washed successively with H_2O, aqueous $NaHCO_3$, H_2O and saturated aqueous NaCl and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue purified by flash chromatography on silica gel (eluant: EtOAc/hexane, 10-20%) to afford the title compound as a yellow oil (24.5 g, 91%). Anal. Calc. for $C_{30}H_{30}O_9$: C, 67.41; H, 5.66;. Found: C, 67.21; H, 5.66.

SEPARATION

Separation of (+) and (-) methyl (1RS)-1-Hydroxy-1-(4-methoxy-2-methoxymethoxyphenyl)-3-(3,4-methylenedioxyphenyl)-6-(prop-1-yloxy)indene-2-carboxylate was done on a column of cellulose tris(3,5-dimethylphenyl carbamate) coated on silica gel (Daicel Chiralcel OD); retention time for (+) 8.8 min. $[\alpha]^{25}_D$= +87.5° (c = 0.24, CH_3OH). Retention time for (-) 14.5 min. $[\alpha]^{25}_D$= +85.9° (c = 0.21, CH_3OH)

HPLC data: column Chiralcel OD (DAICEL) 21.2 mm internal diameter, 250 mm length; solvent Ethanol:Hexane 60:40; flow rate 10 mL/min.; injection: 1 g of racemate; detection UV = 405 nm

g) (+)Methyl (1S,2S,3S)-3-(4-Methoxy-2-methoxymethoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate. A parr vessel was charged with (+) methyl (1RS)-1-Hydroxy-1-(4-methoxy-2-methoxymethoxyphenyl)-3-(3,4-methylenedioxyphenyl)-6-(prop-1-yloxy)indene-2-carboxylate (1 g, 1.8 mmol) dissolved in a small volume of EtOAc (25 mL) and 10% palladium on activated carbon (93 mg). The resulting solution was stirred under an atmosphere of hydrogen for 120 hours and filtered. The filtrate was concentrated under reduced pressure and the product purified by column

chromatography on silica gel (eluant: EtOAc/hexane, 5-10%) to give the title compound as a white foam (0.80 g, 83%). $[\alpha]^{25}_D$= +105.4° (c = 0.13, CH_3OH). Anal. Calc. for $C_{30}H_{32}O_8$: C, 69.22; H, 6.20. Found: C, 68.95; H, 6.11.

h) (+)Methyl (1S,2S,3S)-3-(2-Hydroxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate. To a solution of methyl (1S,2S,3S)-3-(4-Methoxy-2-methoxymethoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate (0.7 g, 1.3 mmol) in methanol (10 mL) concentrated HCl (0.1 mL) was added and it was then heated to reflux for 2 h. The solvent was then eliminated under vacuum and the residue was purified by column chromatography on silica gel (eluant: EtOAc/hexane, 10-20%) to give the title compound as a colorless glass (0.50 g, 78%). $[\alpha]^{25}_D$= +116.0° (c = 0.18, CH_3OH). Anal. Calc. for $C_{28}H_{28}O_7.1/2\ H_2O$: C, 69.27; H, 6.02. Found: C, 69.59; H, 5.99.

i) (+) Methyl (1S,2S,3S)-3-(2-Carboethoxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate. A solution of methyl (1S,2S,3S)-3-(2-hydroxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate (0.1 g, 0.2 mmol) in dry DMF (2 mL) was added to NaH (6 mg, 0.24 mmol) in a small volume of dry DMF at 0°C. The mixture was stirred at 0°C for 15 min. and ethyl bromoacetate was then added (42 mg, 0.25 mmol). The resulting mixture was stirred at 0°C for 1h. The reaction was then quenched with dilute HCl and extracted with EtOAc. The EtOAc extract was washed with water then brine, dried ($MgSO_4$), filtered and evaporated. The product was purified by column chromatography on silica gel (eluant: EtOAc/hexane, 10-15%) to give the title compound as a glassy solid (82 mg, 68%).$[\alpha]^{25}_D$= +116.0° (c = 0.45, CH_3OH). Anal. Calc. for $C_{32}\ H_{34}O_9$: C, 68.32; H, 6.09. Found: C, 67.98; H, 6.09.

j) (+) (1S,2R,3S)-3-(2-Carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid. To a solution of methyl (1S,2S,3S)-3-(2-carboethoxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate (20 mg, 0.04 mmol) in dioxane (1 mL) was added 3 M NaOH solution (0.3 mL, 1 mmol). The reaction mixture was heated to reflux for 4 h and after cooling the solvent was eliminated in vacuo dissolved in water and acidified with 3N HCl. The resulting precipitate was collected by filtration and dried to give a white solid (15 mg, 81%); m.p. 99-102°C

$[\alpha]^{25}_D$= +38.1° (c = 0.22, CH_3OH). Anal. Calc. for $C_{29}H_{28}O_9$: C, 66.92; H, 5.42. Found C, 67.37; H, 5.32.

EXAMPLE 1A

Preparation of 1-Bromo-4-methoxy-2-methoxymethoxybenzene.

a) 1-Bromo-2-hydroxy-4-methoxybenzene. 3-Bromo-2-hydroxy-6-methoxybenzoic acid [T: de Paulis et. al. ,J. Med. Chem., (1985), 28, 1263-1269] (5 g, 0.02 mol) was heated in quinoline (200 mL) at 160°C for 1 h. On cooling, the product was partitioned between Et_2O and 3M HCl. The organic extract was washed with water and brine then dried ($MgSO_4$), filtered and evaporated to give the title compound which was recrystallized from 5% ethyl acetate/hexane (4 g, 97%); m.p. 40-42°C . Anal. Calc. for $C_7H_7BrO_2$: C, 41.41; H, 3.48. Found C, 41.39; H, 3.37.

b) 1-Bromo-4-methoxy-2-methoxymethoxybenzene. To a suspension of NaH (2.5 g, 0.06 mol) in dry DMF (100 mL) at 0°C was added solution of 1-bromo-2-hydroxy-4-methoxybenzene (10.6 g, 0.05 mol). After stirring at 0°C for 30 min. bromomethyl methyl ether (7.8 g, 0.06 mmol) were dropwise added. The mixture was warmed to room temperature over 20 min. and then stirred for 2 h, it was then quenched cautiously by the addition of cold dilute HCl and extracted with EtOAc. The EtOAc extract was washed successively with; H_2O, 5% aqueous $NaHCO_3$, H_2O and finally brine. After drying ($MgSO_4$) filtration and evaporation gave liquid. The product was purified by distillation (85°C, 0.2 mm Hg) to give the title compound as a colorless oil (13.7 g, 97%).
^1H NMR ($CDCl_3$) δ 7.40 (d, 1 H, J = 8.9 Hz), 6.75 (d, 1 H, J = 2.8 Hz), 6.46 (dd, 1 H, J = 8.9, 2.8 Hz), 5.23 (s, 2 H), 3. 77 (s, 3 H), 3.52 (s, 3 H).

EXAMPLE 2

(1RS, 2SR, 3RS)-3-[2-(2-Hydroxyeth-1-yloxy)-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid, dicyclohexylamine salt

m.p. 182-184°C.
Anal. Calc. for $C_{41}H_{53}NO_8$: C, 71.59; H, 7.77; N, 2.04. Found: C, 71.67; H, 7.66; N, 2.42.

EXAMPLE 2A

(+) (1S, 2R, 3S)-3-[2-(2-Hydroxyeth-1-yloxy)-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid

a) (+) Methyl-(1S, 2R, 3S)-3-[2-(2-*t*-Butyldimethylsiloxyeth-1-yloxy)-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate. A solution of methyl-(1S,2S,3S)-3-(2-hydroxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate (3 g, 6 mmol) in dry DMF (30 mL) was added to NaH (230 mg, 7 mmol, 80%) in a small volume of dry DMF at 0°C. The mixture was stirred at 0°C for 15 min. and 2-*t*-butyldimethylsiloxyethylbromide was then added dropwise (1.65 g, 8 mmol). The resulting mixture was stirred at 0°C for 3 h. The reaction was then quenched with dilute HCl and extracted with EtOAc. The EtOAc extract was washed with water then brine, dried ($MgSO_4$), filtered and evaporated. The product was purified by column chromatography on silica gel (eluant: EtOAc/hexane, 5-10%) to give the title compound as a colorless oil (520 mg, 18% based on recovery of epimerized starting material).

b) Methyl-(+) (1S, 2R, 3S)-3-[2-(2-Hydroxyeth-1-yloxy)-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate. To a solution of (+) methyl-(1S, 2R, 3S)-3-[2-(2-*t*-butyldimethylsiloxyeth-1-yloxy)-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate (0.520 g, 0.74 mmol) in THF (10 mL) at RT, a 1 M solution of tetra-*n*-butylammonium fluoride (2.5 mL) in THF was added. The reaction mixture was stirred at RT for 1 h. After concentration in vacuo, the residue was partitioned between ether/ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography on silica gel (eluant: 20-30% ethyl acetate/hexane) to give the title compound as a colorless foam (0.35 g, 82%).

c) (+) (1S, 2R, 3S)-3-[2-(2-Hydroxyeth-1-yloxy)-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid

To a solution of methyl-(1S,2R,3S)-3-[2-(2-hydroxyeth-1-yloxy)-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate (0.35 g, 0.67 mmol) in methanol/THF 1/2 (15 mL) was added a 0.5 M LiOH solution (5 mL). The reaction mixture was stirred at RT overnight. The solvent was eliminated in vacuo the product dissolved in water and acidified with

3N HCl. The resulting precipitate was collected by filtration and dried to give a white solid (0.31 mg, 91%); m.p. 94-98°C.$[\alpha]^{23}_D$= +73.16° (c = 0.19, CH_3OH) Anal. Calc. for $C_{29}H_{29}O_8Na.11/8\ H_2O$: C, 63.47; H, 5.74. Found: C, 63.39; H, 5.66.

EXAMPLE 3

(1RS, 2SR, 3RS)-3-[2-[(4-Carboxypyridin-3-yl)oxy]-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid disodium salt:

a) Methyl (1RS, 2SR, 3RS)-3-[2-[(4-Formylpyridin-3-yl)oxy]-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate

To a solution of Methyl (1RS, 2SR, 3RS)-3-(2-hydroxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate (300 mg, 0.63 mmol) in DMF (4 mL) was added K_2CO_3 (109 mg, 0.79 mmol) and 3-fluoro-4-formylpyridine (150 mg, 1.2 mmol). The reaction mixture was heated to reflux under argon for 2 h. After cooling to room temperature it was partitioned between 3N HCl and ethyl acetate. The ethyl acetate extract was washed with water, aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue purified by flash column chromatography (silica gel, gradient elution from 10% to 20% ethyl acetate/hexanes) to afford the title compound (128 mg, 42%).

b) Methyl (1RS, 2SR, 3RS)-3-[2-[(4-Carboxypyridin-3-yl)oxy]-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate

To a solution of Methyl (1RS, 2SR, 3RS)-3-[2-[(4-formylpyridin-3-yl)oxy]-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate (128 mg, 0.24 mmol) in t-BuOH (10 mL) was added a solution of $NaClO_2$ (34 mg, 0.28 mmol) and NH_2SO_3H (40 mg, 0.42 mmol) in water (6mL). The reaction mixture was stirred at room temperature for 2 h and partitioned between water and ethyl acetate. The ethyl acetate extract was washed with water and brine and dried ($MgSO_4$). The solvent was removed *in vacuo* the residue was purified by flash column chromatography (silica gel, 25% ethyl acetate/hexanes containing 5% of acetic acid) to afford the title compound (90 mg, 69%).

c) (1RS, 2SR, 3RS)-3-[2-[(4-Carboxypyridin-3-yl)oxy]-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid disodium salt

To a solution of Methyl (1RS, 2SR, 3RS)-3-[2-[(4-Carboxypyridin-3-yl)oxy]-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate (90, 0.15 mmol) in isopropanol (2 mL) was added 1M aqueous NaOH (0.3 mL, 0.3 mmol). The resulting mixture was heated to reflux for 12 h, then concentrated under reduced pressure. The residue was partitioned between dilute HCl and ethyl acetate. The ethyl acetate extract was washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, 30% ethyl acetate/hexanes containing 5% of acetic acid) to afford the title compound (65 mg, 74%); m.p. 220-222°C (dec.) (disodium salt).

EXAMPLE 4

2,2-Dimethylpropanoyloxymethyl (1RS,2SR,3RS)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate sodium salt

a) 2,2-Dimethylpropanoyloxymethyl (1RS,2SR,3RS)-3-(2-hydroxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate

(1RS,2SR,3RS)-3-(2-hydroxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid potassium salt (125 mg, 0.54 mmol) (obtained by treatment of the corresponding acid with $KHCO_3$ (54 mg, 0.54 mmol)) was dissolved in DMF (3 ml) and pivaloyloxymethyl iodide (0.54 mmol) (prepared from pivaloyloxymethyl chloride (73 mg, 0.54 mmol) and excess sodium iodide in acetone) added. The reaction mixture was stirred overnight and then partitioned between dil. HCl and ethyl acetate. The organic layer was washed with water and brine then dried ($MgSO_4$ anhyd.) filtered and evaporated. The product was purified by column chromatography to provide the title compound (120 mg, 77%) as a colorless oil.

b) 2,2-Dimethylpropanoyloxymethyl (1RS, 2SR, 3RS)-3-(2-carbobenzyloxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate.

2,2-Dimethylpropanoyloxymethyl (1RS,2SR,3RS)-3-(2-hydroxy-

4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate (280 mg, 0.5 mmol) in dry DMF (3 ml) was added to NaH (18 mg, 0.6 mmol) in a small volume of dry DMF. The mixture was stirred at RT for 20 min. then benzyl bromoacetate (137 mg, 0.6 mmol) was added. After stirring for 1.5 h the product was partitioned between 3M aqueous HCl and ethyl acetate. The organic layer was washed with water then brine, dried ($MgSO_4$ anhyd.) filtered and evaporated to give an oil. The product was purified by column chromatography to provide the title compound (240 mg, 66%) as a colorless oil.

c) 2,2-Dimethylpropanoyloxymethyl (1RS,2SR,3RS)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid.

2,2-Dimethylpropanoyloxymethyl (1RS,2SR,3RS)-3-(2-carbobenzyloxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate (240 mg, 0.3 mmol) was dissolved in a 2:1 mixture of ethyl acetate and ethanol (3 ml) and then 50 mg of 10%Pd/C was added. The mixture was stirred at room temperature under an H_2 atmosphere for 3 h. The catalyst was then filtered, the solvent concentrated *in vacuo* and the resultant oil purified by flash column chromatography. The title compound was obtained (180 mg, 86%) as a colorless oil.

MS (exact mass) $(M+Na)^{+\cdot}$: 647.2335 (sodium salt)
(D = -2.3. mDa for $C_{33}H_{38}O_{11}Na$)
mp 190-195°C (dec, sodium salt)

EXAMPLE 5

(1S, 2R, 3S)-3-[2-[Carbo-(1RS)-1-(2-methoxy-2-methylpropionyloxy)eth-1-yloxymethoxy]-4-methoxyphenyl-1-(3,4-methlenedioxyphenyl)-5-prop-1-yloxy)indane-2-carboxylic acid sodium salt

a) Allyl (1S, 2R, 3S)-3-(4-methoxy-2-methoxymethoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate.

(1S, 2R, 3S)-3-(4-methoxy-2-methoxymethoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid (4.8 g, 9.5 mmol) was dissolved in dry acetonitrile (30 ml) and DBU (1.7 ml, 11.4 mmol) was added followed by allyl bromide (3.4 g, 28. mmol). After stirring for 0.5 h. the product was partitioned between 3M aqueous HCl and ethyl acetate. The organic layer was washed with water and brine, then dried ($MgSO_4$ anhyd.)

filtered and evaporated to give an oil. The product was purified by column chromatography to provide the title compound as a pale yellow oil (5.7 g, quantitative).

b) Allyl (1S, 2R, 3S)-3-(2-hydroxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate.

Allyl (1S, 2R, 3S)-3-(4-methoxy-2-methoxymethoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate (1.7 g, 3.11 mmol) was dissolved in allyl alcohol (20 ml) and then 15 drops of conc. HCl was added. The resulting solution was stirred at 65°C for 2 h. After removing the solvent the residue was partitioned between water and ethyl acetate. The organic layers were washed with water, 5% aqueous $NaHCO_3$ and brine; then dried ($MgSO_4$ anhyd.), filtered and evaporated to give an oil. The product was purified by column chromatography to provide the title compound as a pale yellow oil (1.26 g, 81%).

c) Allyl (1S, 2R, 3S)-3-(2-Carbo-1-*tert*-butoxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate.

Allyl (1S, 2R, 3S)-3-(2-Hydroxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate (1.0 g, 2 mmol) in dry DMF (4 ml) was added to NaH (57 mg, 2.4 mmol) in a small volume of dry DMF. The mixture was stirred at RT for 20 min., then *tert*-butyl bromoacetate (974 mg, 5 mmol) was added. After stirring for 0.5 h., the product was partitioned between 3M aqueous HCl and ethyl acetate. The organic layer was washed with water, brine and dried ($MgSO_4$ anhyd.), filtered and evaporated to give an oil. The product was purified by column chromatography to provide the title compound (1.1 g, 93%) as a pale yellow oil.

d) Allyl (1S, 2R, 3S)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate.

Allyl (1S, 2R, 3S)-3-(2-carbo-tert-butoxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate (765 mg, 1.24 mmol) was dissolved in TFA (5 ml) containing a few drops of anisole. The reaction mixture was stirred at RT for 20 min. The solvent was eliminated, the residue was diluted with ethyl acetate, washed with

water, brine and dried ($MgSO_4$ anhyd.), filtered and evaporated. The product was purified by column chromatography to provide the title compound (575 mg, 83%) as a colorless oil.

e) Allyl (1S, 2R, 3S)-3-[2-[Carbo-(1RS)-1-(2-methoxy-2-methylpropionyloxy)eth-1-yloxymethoxyl-4-methoxyphenyl-1-(3,4-methlenedioxyphenyl)-5-prop-1-yloxy)indane-2-carboxylic acid sodium salt

Allyl (1S, 2R, 3S)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate (287 mg, 0.5 mmol) was dissolved in DMF (5 ml) and Cs_2CO_3 (333 mg, 1 mmol) added followed by (1S)-1-bromoethyl 2-methoxy-2-methylpropionate (225 mg, 1 mmol). The reaction mixture was stirred at RT overnight, then partitioned between water and ethyl acetate, washed with dil. HCl and brine, dried ($MgSO_4$ anhyd.), filtered and evaporated to give an oil. The product was purified by column chromatography to provide the title compound (260 mg, 74 %) as a colorless oil.

f) (1S, 2R, 3S)-3-[2-[Carbo-(1RS)-1-(2-methoxy-2-methylpropionyloxy)eth-1-yloxymethoxy]-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-prop-1-yloxy)indane-2-carboxylic acid sodium salt

Allyl (1S,2R,3S)-3-[2-Carbo-(1RS)-1-(2-methoxy-2-methylpropionyloxyeth-1-yloxymethoxy]-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate (260 mg, 0.37 mmol) was dissolved in CH_2Cl_2 (2 ml) and tetrakis(triphenylphosphine)palladium(0) (36 mg, 0.037 mmol) added followed by tri-*n*-butyltin hydride (0.11 ml, 0.4 mol). The reaction mixture was stirred at RT for 3 h then quenched with 3N HCl and stirred for 20 min. The organic layer was diluted with ethyl acetate washed with water then brine, dried ($MgSO_4$ anhyd.), filtered and evaporated to give an oil. The product was purified by column chromatography to provide the title compound (210 mg, 85 %) as a colorless oil.

MS (exact mass) $(M+Na)^{+\cdot}$: 687.2415 (sodium salt)

(D = +0.3. mDa for $C_{36}H_{40}O_{12}Na$)

By the methods given above, the following compounds were made.

(1RS, 2SR, 3RS)-3-[2-[(3-Carboxypyridin-2-yl)oxy]-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid,
m.p. 152-155°C

(1RS, 2SR, 3RS)-3-[2-[Carbo(N,N-diethylcarbamoyl)methoxy]methoxy-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid,
m.p. 181-182°C;

Trans, Trans-1,3-Bis(4-methoxyphenyl)indane-2-carboxamide,
m.p. 223-225°C;

(1RS,2SR,3SR)-3-[4-Methoxy-2-[2-(methylphosphinyl) eth-1-yl]phenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid disodium salt;
(exact mass) M^++Na: 619.1462 (Δ = -1.2 mDa for $C_{30}H_{31}O_8PNa_3$)

EXAMPLES 6-30

Indan-5-yl (1RS,2SR,3RS)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate sodium salt,
m.p. 181-183°C dec.

3, 5-Dimethoxyphenyl (1RS,2SR,3RS)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate sodium salt
m.p. 185-189°C dec.

(1RS)-1- (2-Methoxy-2-methylpropionyloxy)eth-1-yl (1RS,2SR,3RS)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate sodium salt
m.p. 178-181°C dec.

N,N-Dimethylcarbamoylmethyl (1RS,2SR,3RS)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate sodium salt

m.p. 170-174°C dec.

Ethoxycarboxymethyl (1RS,2SR,3RS)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate sodium salt

MS (exact mass) $(M+Na)^{+\cdot}$: 645.1959 (sodium salt)
(D = -1.1 mDa for $C_{33}H_{34}O_{12}Na$)

Benzoyloxymethyl (1RS,2SR,3RS)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate sodium salt

MS m/e : 672 $(M+NH_4)^+$

Cyclohexyloxycarboxymethyl (1RS,2SR,3RS)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate sodium salt

MS (exact mass) $(M+Na)^{+\cdot}$: 699.2453 (sodium salt)
(D = -3.5. mDa for $C_{37}H_{40}O_{12}Na$)

Ethyl (1RS,2SR,3RS)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate sodium salt

MS (exact mass) $M^{+\cdot}$: 548.2040 (free acid)
(D = +0.6. mDa for $C_{31}H_{32}O_9$)

(1S,2R,3S)-3-[2-[Carbo-(2',6'-dimethylphenoxy)methoxyl-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid sodium salt

MS (exact mass) $(M+Na)^{+\cdot}$: 647.2264 (sodium salt)
D = -0.7. mDa for $C_{37}H_{36}O_9Na$)

(1S,2R,3S)-3-[2-(Carbocyclopentyloxymethoxy)-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid sodium salt

MS (exact mass) $(M+Na)^{+\cdot}$: 611.2282 (sodium salt)
(D = -2.5. mDa for $C_{34}H_{36}O_9Na$)

(1S,2R,3S)-3-[2-[Carbo(indan-5-yloxy)methoxy]-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid sodium salt

MS (exact mass) $(M+Na)^{+\cdot}$: 659.2281 (sodium salt)

(D = -2.4. mDa for $C_{38}H_{36}O_9Na$)

(1S,2R,3S)-3-[2-Carbo(eth-1-yloxy)methoxy]-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid sodium salt

MS (exact mass) $(M+2Na-H)^{+\cdot}$: 593.1769 (sodium salt)

(D = -0.6 mDa for $C_{31}H_{31}O_9Na_2$)

(1RS,2SR,3RS)-3-(2-Carboethoxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid

m.p. 148-149°C.

(1RS, 2SR, 3RS)-2-Trifluoromethylsulfonamidomethyl-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane

m.p. 184-186°C

Indan-5-yl (1S,2R,3S)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate sodium salt

Cyclopentyl (1S,2R,3S)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate sodium salt.

Ethoxycarboxymethyl (1S,2R,3S)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate sodium salt.

(1RS)-1-(1-Methylethoxycarboxy)eth-1-yl (1RS,2SR,3RS)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate sodium salt.

m.p. 151-155°C.

Ethyl (1S,2R,3S)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylate sodium salt

(1S,2R,3S)-3-[2-Carbomethoxymethoxy-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid sodium salt

(1S,2R,3S)-3-[2-[Carbobenzoyloxymethoxymethoxy]-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid sodium salt

(1S,2R,3S)-3-[2-(Carboethoxycarboxyloxymethoxymethoxy)-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid sodium salt

(1S,2R,3S)-3-[2-(Carboacetoxymethoxymethoxy)-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid sodium salt

(1S,2R,3S)-3-[2-[Carbophthalidylmethoxy)-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid sodium salt

(1S,2R,3S)-3-[2-Carbo-(2-methoxy-2-methylpropionyloxymethoxymethoxy]-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid sodium salt

EXAMPLE 31

(1S,2R,3S)-3-[2-Carbo-(2,2-dimethylpropanoyloxymethoxymethoxy]-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid sodium salt

To a solution of (1S,2R,3S)-3-[2-Carboxymethoxy-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid monopotassium salt (170 mg, 0.3 mmol) (obtained by treatment of the corresponding diacid (156 mg, 0.3 mmol) with 1 equiv. of $KHCO_3$ (30 mg, 0.3 mmol)) in DMF (4 mL) pivaloyloxymethyl iodide (74 mg, 0.3 mmol) was added. The reaction mixture was stirred at RT for 0.5 h and more pivaloyloxymethyl iodide was then added (20 mg. 0.08 mmol) and then stirred for an additional 0.5 h. The reaction mixture was partitioned between dilute aqueous HCl and ethyl acetate. The ethyl acetate extract was washed with water and brine and dried ($MgSO_4$ anhydrous). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography

(silica gel, Ethyl Acetate/hexane/HOAc 30/65/5) to obtain the desired compound as a white foam (140 mg, 73 %) as the free acid which was converted to its sodium salt. m.p. 128 - 133°C.

MS (exact mass) M^++Na : 679.2116 (sodium salt)

(D = +1.2 mDa for $C_{35}H_{37}O_{11}Na_2$)

EXAMPLE 32

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Inhalant Formulation

A compound of Formula I, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

Tablets/Ingredients		Per Tablet
1.	Active ingredient (Cpd of Form. I)	40 mg
2.	Corn Starch	20 mg
3.	Alginic acid	20 mg
4.	Sodium Alginate	20 mg
5.	Mg stearate	1.3 mg
		2.3 mg

Procedure for tablets:

Step 1 Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2 Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3 The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4 The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5 The dry granules are lubricated with ingredient No. 5.

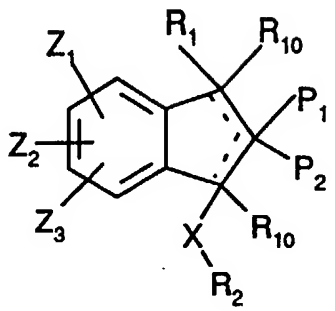
Step 6 The lubricated granules are compressed on a suitable tablet press.

Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then steriled by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

CLAIMS:

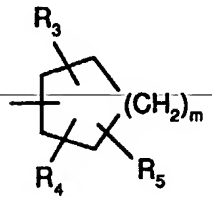
1. A compound of Formula (I):



(I)

wherein:

R_1 is $-X(CH_2)_nAr$ or $-X(CH_2)_nR_8$ or



(c) ;

R_2 is hydrogen, Ar, C_{1-4}alkyl or (c);

P_1 is $-X(CH_2)_nR_8$;

P_2 is $-X(CH_2)_nR_8$, or $-X-R_9-Y$;

R_3 and R_5 are independently hydrogen, R_{11}, OH, C_{1-8}alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, Br, F, I, Cl, CF_3, $NHCOR_6$, $R_{11}CO_2R_7$, $-X-R_9-Y$, or $-X(CH_2)_nR_8$ wherein each methylene group within $-X(CH_2)_nR_8$ may be unsubstituted or substituted by one or two $-(CH_2)_nAr$ groups;

R_4 is hydrogen, R_{11}, OH, C_{1-5}alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, $-X(R_{11})$, Br, F, I, Cl or $NHCOR_6$ wherein the C_{1-5}alkoxy may be unsubstituted or substituted by OH, methoxy or halogen;

R_6 is independently hydrogen or C_{1-4}alkyl;

R_7 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-8} alkynyl, all of which may be unsubstituted or substituted by one or more OH,

$N(R_6)_2$, CO_2R_{12}, halogen or XC_{1-5}alkyl; or R_7 is $(CH_2)_nAr$;

R_8 is hydrogen, R_{11}, CO_2R_7, $CO_2C(R_{11})_2O(CO)XR_7$, $PO_3(R_7)_2$, $SO_2NR_7R_{11}$, $CONR_7SO_2R_{11}$, SO_3R_7, SO_2R_7, $P(O)(OR_7)R_7$, CN, $C(O)N(R_6)_2$, $-CO_2(CH_2)_mC(O)N(R_6)_2$, $C(R_{11})_2N(R_7)_2$, tetrazole or OR_6;

R_9 is $(CH_2)_n$, divalent C_{1-10}alkyl, divalent C_{2-10}alkenyl or phenyl, all of which may be unsubstituted or substituted by one or more OH, $N(R_6)_2$, COOH, halogen, or may be)C=O or XC_{1-5}alkyl;

R_{10} is R_3 or R_4;

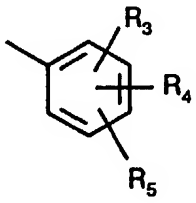
R_{11} is hydrogen, Ar, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, all of which may be unsubstituted or substituted by one or more OH, CH_2OH, $N(R_6)_2$ or halogen;

R_{12} is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-7}alkynyl;

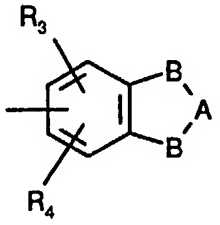
X is $(CH_2)_n$, O, NR_6 or $S(O)_q$;

Y is CH_3 or $X(CH_2)_nAr$;

Ar is:



(a)



(b)

naphthyl, indolyl, pyridyl, thienyl, oxazolidinyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, or pyrimidyl; all of which may be unsubstituted or substituted by one or more R_3 or R_4 groups;

A is C=O, or $[C(R_6)2]_m$;

B is $-CH_2-$ or -O-;

Z_1 and Z_2 are independently hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, OH, C_{1-8}alkoxy, $S(O)qC_{1-8}$alkyl, $N(R_6)_2$, Br, F, I, Cl, $NHCOR_6$, $-X-R_9-Y$, $-X(CH_2)_nR_8$, phenyl, benzyl or C_{3-6}cycloalkyl wherein the C_{1-8}alkyl, C_{2-8}alkenyl or C_{2-8}alkynyl may be optionally substituted by COOH, OH,

$CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R_6)_2$, or halogen; or Z_1 and Z_2 together may be -O-A-O- on contiguous carbons;

Z_3 is Z_1 or -X-R_9-Y;

q is zero, one or two;

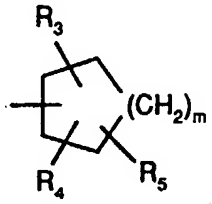
n is an integer from 0 to six;

m is 1, 2 or 3;and the dotted line indicates the optional presence of a double bond; or a pharmaceutically acceptable salt thereof; provided that

- R_2 is not hydrogen when X is $S(O)_q$;
- when the optional double bond is present there is only one R_{10} and there is no P_1 and P_2 is not NR_6R_9Y;
- when the optional double bond is present in Formula (I) and X-R_2 is attached to the double bond, X is not NR_6;
- when the optional double bond is present and R_1 is attached directly to the double bond, R_1 is not NR_6AR;
- when R_3, R_5, Z_1, Z_2, or Z_3 is $X(CH_2)_nR_8$ and n is not 0, X is oxygen or NR_6 when R_8 is OR_6 or CO_2H;
- when R_8 is $CO_2C(R_{11})_2O(CO)XR_7$, X is not $S(O)_q$;
- the compound of Formula I is not (1RS)-1,3-diphenylindene-2-carboxylic acid; (cis,cis)-(1RS,3SR)-1,3-diphenylindane-2-carboxylic acid; (1RS)-3-[3-Methyl-1-phenyl-(1H)-ind-2-en-1-yl] propionic acid; or (1RS)-2[1,3-diphenyl-(1H)-ind-2-en-2-yl]ethanoic acid; 1,3-diphenyl-1-ethoxyindene-2-carboxylic acid; 1,2,3-triphenylindene; 1,3 diphenylindene; 1-(2,3-dimethyl-2-buten-yl)-1,3-diphenylindene; 1,3-diphenyl-2-methylindene; 1,3-diphenyl-2-methylindane; 1,3-diphenylindane; 5,6-dimethoxy-1,3-dimethoxyindene; 1,3-bis(4,5-dimethoxy-2-hydroxyphenyl)-5,6-dimethoxyindane; 1,3-bis(3,4-dimethoxyphenyl)-5,6-dimethoxyindane; 1,3-diphenyl-2-methoxyidene, 1,3-diphenyl-2-ethoxyindene, or 5-fluoro-2-methyl-indene-3-acetic acid;

and further provided that compounds wherein:

R_1 is -$X(CH_2)_nAr$ or -$X(CH_2)_nR_8$ or



(c);

R_2 is hydrogen, Ar or (c);

P_1 is $-X(CH_2)_nR_8$;

P_2 is $-X(CH_2)_nR_8$, or $-XR_9Y$;

R_3 and R_5 are independently hydrogen, R_{11}, OH, C_{1-8}alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, Br, F, I, Cl, CF_3, $NHCOR_6$, $-XR_9-Y$ or $-X(CH_2)_nR_8$ wherein the methylene groups of $-X(CH_2)_nR_8$ may be unsubstituted or substituted by one or more $-(CH_2)_nAr$ groups;

R_4 is hydrogen, R_{11}, OH, C_{1-5}alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, $-X(R_{11})$, Br, F, I, Cl or $NHCOR_6$ wherein the C_{1-5}alkoxy may be unsubstituted or substituted by OH, methoxy or halogen;

R_6 is independently hydrogen or C_{1-4}alkyl;

R_7 is independently hydrogen, C_{1-6}alkyl or $(CH_2)_nAr$;

R_8 is hydrogen, R_{11}, CO_2H, PO_3H_2, $P(O)(OH)R_7$ or tetrazole;

R_9 is C_{1-10}alkyl, C_{2-10}alkenyl or phenyl all of which may be unsubstituted or substituted by one or more OH, $N(R_6)_2$, COOH, halogen or XC_{1-5}alkyl;

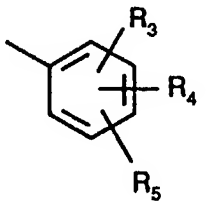
R_{10} is R_3 or R_4;

R_{11} is C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl all of which may be unsubstituted or substituted by one or more OH, CH_2OH, $N(R_6)_2$ or halogen;

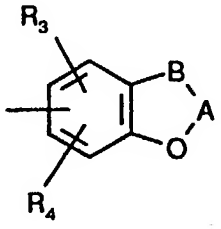
X is $(CH_2)_n$, O, NR_6 or $S(O)_q$;

Y is CH_3 or $-CH_2X(CH_2)_nAr$;

Ar is:



(a)



(b)

naphthyl, indolyl, pyridyl or thienyl, oxazolidinyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl,

or pyrimidyl; all of which may be unsubstituted or substituted by one or more R_3 or R_4 groups;

A is C=O, or $[C(R_6)_2]_m$;

B is $-CH_2-$ or -O-;

Z_1 and Z_2 are independently hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, OH, C_{1-8}alkoxy, $S(O)qC_{1-8}$alkyl, $N(R_6)_2$, Br, F, I, Cl, $NHCOR_6$, $-X(CH_2)_nR_8$, phenyl, benzyl or C_{3-6}cycloalkyl wherein the C_{1-8}alkyl, C_{2-8}alkenyl or C_{2-8}alkynyl may be optionally substituted by COOH, OH, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R_6)_2$, or halogen; or Z_1 and Z_2 together may be -O-A-O- on contiguous carbons;

Z_3 is Z_1 or XR_9Y;

q is zero, one or two;

n is an integer from 0 to six;

m is 1, 2 or 3; are excluded.

2. A compound of Claim 1 wherein R_1 is $X(CH_2)_nAr$, dihydrobenzofuranyl, benzodioxanyl, cyclohexyl, or C_{1-4}alkyl; R_2 is a moiety of formula (a) or (b), C_{1-4}alkyl, indolyl or hydrogen; R_3 and R_5 are independently hydrogen, OH, C_{1-5}alkoxy, halogen, $-OC_{1-4}$alkyl phenyl, $R_{11}CO_2R_7$, C_{1-4}alkyl, $N(R_6)_2$, $NH(CO)CH_3$, $-X(CH_2)_nR_8$, -X-R_9-Y, pyridyl, phenyl or $S(O)qC_{1-5}$alkyl; R_4 is hydrogen, OH, C_{1-5}alkoxy, halogen, C_{1-4}alkyl, $N(R_6)_2$, $NH(CO)CH_3$ or $S(O)qC_{1-5}$alkyl; Z_1, Z_2 and Z_3 are independently X-R_9-Y, benzyl, hydrogen, OH, C_{1-5}alkoxy, $-N(R_6)_2$, $S(O)_qC_{1-8}$alkyl, $NHCOR_6$, $X(CH_2)_nR_8$ or halogen, or Z_1 and Z_2 together may be -O-A-O on contiguous carbons; P_1 and P_2 are independently hydrogen, CO_2H or tetrazole; Ar is a moiety of formula (a), or (b), phenyl, or pyridyl and X is $(CH_2)_n$ or oxygen.

3. A compound of Claim 2 wherein R_3 is hydrogen, $-X(CH_2)_nR_8$ or $R_{11}CO_2R_7$; R_4 and R_5 are independently hydrogen, OH, C_{1-5}alkoxy, SC_{1-5}alkyl, substituted phenyl, F, Br, C_{1-3}alkyl or NH_2; Z_1 and Z_3 are hydrogen and Z_2 is hydrogen, OH, C_{1-5}alkoxy, halogen, $X(CH_2)_nR_8$, NH_2, benzyl or $NH(CO)CH_3$, or Z_1 and Z_2 together may be O-A-O on contiguous carbons.

4. A compound of Claim 3 wherein R_1 is a moiety of formula (b) and R_2 is a moiety of formula (a) or (b); A is CH_2, B is -O-; there is no optional double bond; R_1 and XR_2 are trans to P_1; Z_2 is OH, C_{1-5}alkoxy, $-OCH_2CHCH_3$ or

hydrogen, Z_1 is hydrogen; R_3 is hydrogen, XAr, $X(CH_2)_qCO_2H$, $X(CH_2)_qCONR_7SO_2R_{11}$, or $CH{=}CHCO_2H$, R_4 is hydrogen, substituted phenyl, or C_{1-2}alkoxy; and R_5, R_{10} and P_2 are hydrogen.

5. A compound selected from the group consisting of:

(+)(1RS, 2SR, 3SR)-3-(2-Carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxyy)indane-2-carboxylic acid; and

(+)(1RS, 2RS, 3SR)-3[2-(2-Hydroxyeth-1-yloxy)-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid;

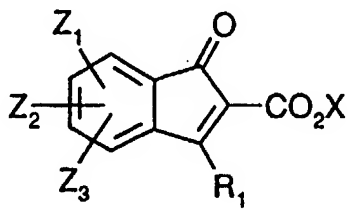
(1RS, 2RS, 3SR)-3-[2-[(4-Carboxypyridin-3yl)oxy]-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid disodium.

6. A pharmaceutical composition comprising a compound of Claim 1 or Claim 5 and a pharmaceutically acceptable carrier.

7. A method of antagonizing endothelin receptors which comprises administering to a subject in need thereof, an effective amount to antagonize endothelin receptors of a compound of Claim 1 or Claim 5.

8. A method of treating hypertension, renal failure or cerebrovascular disease which comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1 or Claim 5.

9. A process for the preparation of a compound of formula (I) of Claim 1 or Claim 5 a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (II)

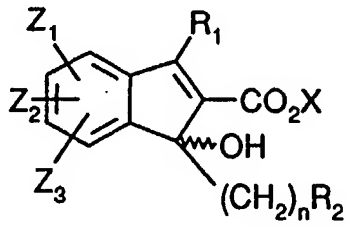


(II)

wherein Z_1, Z_2, Z_3 and R_1 are as described in claim 1 or a group convertable thereto, and X is alkyl, with an organomagnesium compound of formula (III)

$$R_2\text{-}(CH_2)_n\text{-}MgBr \qquad \text{(III)}$$

wherein R_2 is as described in claim 1 or a group convertable thereto, in a suitable solvent to provide a compound of formula (IV)



(IV)

which is reduced and thereafter, when desired or necessary undergoes,

a) insertion of R_{10} (when other than hydrogen) through conjugate additon; and/or

b) alkylation or acylation to give compounds wherein P_1 and P_2 are other than CO_2H; and/or

c) conversion R_1, R_2, Z_1, Z_2 and Z_3;

to afford a compound of formula (I).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/04603

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOLUME 59, ISSUED NOVEMBER 1986, (TOKYO, JAPAN), KIMIAKI YAMAMURA ET AL., "FORMATION OF 2-SUBSTITUTED 1,3-DIPHENYLINDENES BY AN N-BROMOSUCCINIMIDE PROMPTED DEHROCYCLIZATION OF 2-SUBSTITUTED 1,3,3-TRIPHENYL-1-PROPENES", PAGES 3699-3701, SEE ENTIRE DOCUMENT.	1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 25 JULY 1994	Date of mailing of the international search report 0 1 AUG 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer NICKY CHAN Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/04603

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (5):

A61K 31/075, 31/165, 31/185, 31/18, 31/19, 31/21, 31/335, 31/34, 31/35, 31/36, 31/365;
C07C 61/20, 62/32, 69/74, 309/25, 309/63, 311/14;C07D 317/50; C07F 9/30, 9/38.

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/75, 100, 450, 456, 464, 469, 530, 569, 602, 617, 717; 549/220, 221, 307, 310, 355, 401, 404, 447, 466, 467;
558/44, 45; 560/10, 43, 45, 48, 56; 562/8, 11, 15, 23, 24, 25, 100, 428, 451, 452, 455, 467; 564/84,180; 568/659.

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

514/75, 100, 450, 456, 464, 469, 530, 569, 602, 617, 717; 549/220, 221, 307, 310, 355, 401, 404, 447, 466, 467;
558/44, 45; 560/10, 43, 45, 48, 56; 562/8, 11, 15, 23, 24, 25, 100, 428, 451, 452, 455, 467; 564/84,180; 568/659.